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10/525,643	03/06/2006	George Coukos	555-88	7985

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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/525,643	COUKOS ET AL.	
	Examiner	Art Unit	
	DiBrino Marianne	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *2/25/05,3/6/06,6/30/06*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) *1-8,11 and 19-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9,10 and 12-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 February 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/27/09,1/13/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendments filed 2/25/05, 3/6/06, 6/30/06 and Applicant's response filed 12/23/08 are acknowledged and have been entered.

2. Applicant is required under 37 C.F.R. 1.821(d) to amend the specification to list the appropriate SEQ ID NO for sequences disclosed in the specification (for example, in the brief description of the drawings for Figure 1F after the occurrence of "Fig. 1F").

3. Applicant's election with traverse of Group II (claims 9-18) and species of nucleic acid sequence encoding the sequence of SEQ ID NO: 8 in Applicant's response filed 12/23/08 is acknowledged.

The basis for Applicant's traversal is of record on pages 1-2 of the said response, briefly that a thorough search of the art relating to Group II would encompass the art relating to all of Groups I and III-VIII, that a thorough search of the art relating to the elected species would encompass the art relating to non-elected species, and thus it is believed that no undue search burden would be placed on the Examiner if all of the claimed subject matter were to be considered in this application.

However, the standard for lack of unity of invention is not undue burden, but rather that the Groups lack the same or corresponding special technical features. The Requirement mailed 6/23/08 meets this criterion at item #1 on pages 2-3. With respect to Applicant's argument to species election, the species are distinct because they have different sequences, and a search of each species involves different search and review criteria.

The requirement is still deemed proper and is therefore made FINAL.

Accordingly, claim 11 (non-elected species of Group II) and claims 1-8 and 19-30 (non-elected groups I and III-VII) are withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to non-elected inventions.

Claims 9, 10 and 12-18 are currently being examined.

4. The use of the trademark TAQMAN has been noted in this application, for example, on page 8 at line 11, page 31 at line 27 and page 42 at line 15. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

5. The abstract of the disclosure is objected to because it does not describe the claimed invention. Correction is required. See MPEP § 608.01(b).

6. The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because: Inventor Conejo-Garcia's written signature does not match his name as it appears on the said declaration.

7. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code, for example on page 25 at lines 19 and 27 and on page 26 at lines 1, 10, 13, 16 and 17. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

8. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which Applicant may become aware in the specification.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 9, 10 and 12-18 are rejected under 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The instant claims encompass an isolated nucleic acid molecule of undisclosed sequence that is a variant of SEQ ID NO: 8 or any fragment of SEQ ID NO: 8 with undisclosed N-and/or -C-terminal sequences. There is insufficient disclosure in the specification on such a nucleic acid molecule encoding a variant or fragment of SEQ ID NO: 8.

The specification discloses that the polypeptide with the amino acid sequence set forth in SEQ ID NO: 8 is "Letal" or "ULBP4" (paragraph spanning pages 10-11). The specification discloses that Letal variants of the invention include polypeptides substantially identical to the sequence of SEQ ID NO: 8, but do not include ULBP 1, 2 or 3, and the variants can include one or more deletions, insertions or conservative or non-conservative substitutions relative to the sequence of SEQ ID NO: 8. The specification further discloses that the variant can have an amino acid sequence that is at least 50%, 60%, 70%, 80%, 90%, 98%, 99% or 99.9% identical to the sequence of SEQ ID NO: 8

(page 11 at the first paragraph). The specification discloses that variants and fragments of the invention include, but are not limited to, polypeptides that retain a biological activity of the Letal polypeptide, for example, the ability to bind NKG2D receptor, an example being about amino acid residue 29 to about amino acid 225 of SEQ ID NO: 8 (paragraph spanning pages 12-13). The specification also discloses that the invention includes nucleic acids comprising sequences that are at least 50%, 60%, 70%, 80%, 90%, 95%, 98%, 99% or 99.9% identical to the sequence of SEQ ID NO: 1-4, the four exons that are present in the Letal genomic sequence (page 15 at the first full paragraph and page 4 at lines 16-21). The specification also discloses that Letal and functional variants and fragments thereof, can be used, for example to enhance proliferation of immunoeffector cells such as NK and NKT cells and/or CTL activity both *in vitro* and *in vivo*, for example against tumors and infectious agents such as viruses and bacteria, or to expand T cells or other effector cells *in vitro* for use in adoptive immunotherapy for patients with cancer and infectious diseases (paragraph spanning pages 17-18).

The guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, § 1 "Written Description" Requirement make clear that if a claimed genus does not show actual reduction to practice for a representative number of species, then the Requirement may be alternatively met by reduction to drawings, or by disclosure of relevant, identifying characteristics, *i.e.,* structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Fri. January 5, 2001, see especially page 1106 column 3).

The court has further stated that "Adequate written description requires a precise definition, such as by structure, formula, chemical name or physical properties, not a mere wish or plan for obtaining the claimed chemical invention." Id. at 1566, 43 USPQ2d at 1404 (quoting Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606). Also see Enzo-Biochem v. Gen-Probe 01-1230 (CAFC 2002).

The specification discloses sequence alignment/identity of SEQ ID NO: 8 with the amino acid sequences of ULBP1, 2 and 3, as well as signal peptide, α1 and α3 domain alignments, but does not disclose what amino acid residues are important for various Letal functional properties. It is noted by the Examiner that the claims do not recite a functional property.

The claims lack adequate written description because the instant disclosure does not provide a representative number of examples of polypeptides comprising the sequence of a variant or fragment of SEQ ID NO: 8, including one that is encoded by a nucleic acid molecule comprising the sequences of nucleotides shown in SEQ ID NOs: 1-4, nor does the specification provide a structure-function correlation for what region(s) is/are required for some type of functional activity, and by extension so does not provide a

representative number of species for the nucleic acid molecule encoding the said variant or fragment.

As such a skilled artisan would reasonably conclude that Applicant was not in possession of the claimed nucleic acid molecule of a genus that includes millions of members at the time the application was filed.

11. Claims 9, 10 and 12-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated nucleic acid molecule that encodes SEQ ID NO: 8 or a nucleic acid molecule complementary thereto, a construct comprising a vector and the said nucleic acid molecule, a host cell comprising said construct, and method of producing said polypeptide by culturing said host cell, does not reasonably provide enablement for a nucleic acid molecule that encodes a variant or fragment of SEQ ID NO: 8 or a nucleic acid molecule complementary thereto, including a nucleic acid molecule that comprises the sequence of nucleotides shown in SEQ ID NOs: 1-4, a construct comprising a vector and the nucleic acid molecule, a host cell comprising said construct, and method of producing said polypeptide by culturing said host cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

"To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" Genentech, Inc. v. Novo Nordisk, A/S, 108F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997) (quoting In re Wright, 999F2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)). In In re Wands 8 USPQ2d 1400 (CAFC 1988), a number of factors are set forth which a court may consider in determining whether a disclosure would require undue experimentation. These factors were set forth as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. All the factors need not be reviewed when determining whether a disclosure is enabling. Amgen, Inc. v. Chugai Pharm. Co., Ltd., 927F2.d 1200, 1213, 18 USPQ2d 1016, 1027 (Fed. Cir. 1991) (noting that the Wands factors "are illustrative, not mandatory. What is relevant depends upon the facts.").

The instant claims encompass an isolated nucleic acid molecule that is a variant of SEQ ID NO: 8 of undisclosed sequence or any fragment of SEQ ID NO: 8 with undisclosed N- and/or -C-terminal sequences. It is noted by the Examiner that no functional property of the encoded polypeptide is recited in the instant claims.

The specification discloses that the polypeptide with the amino acid sequence set forth in SEQ ID NO: 8 is "Letal" or "ULBP4" (paragraph spanning pages 10-11). The specification discloses that Letal variants of the invention include polypeptides substantially identical to the sequence of SEQ ID NO: 8, but do not include ULBP 1, 2 or 3, and the variants can include one or more deletions, insertions or conservative or non-conservative substitutions relative to the sequence of SEQ ID NO: 8, but does not provide working examples of such. The specification further discloses that the variant can have an amino acid sequence that is at least 50%, 60%, 70%, 80%, 90%, 98%, 99% or 99.9% identical to the sequence of SEQ ID NO: 8 (page 11 at the first paragraph). The specification discloses that variants and fragments of the invention include, but are not limited to, polypeptides that retain a biological activity of the Letal polypeptide, for example, the ability to bind NKG2D receptor, some examples are about amino acid residue 29 to about amino acid 225 of SEQ ID NO: 8 (paragraph spanning pages 12-13). The specification also discloses that the invention includes nucleic acids comprising sequences that are at least 50%, 60%, 70%, 80%, 90%, 95%, 98%, 99% or at last 99.9% identical to the sequence of SEQ ID NO: 1-4, the four exons that are present in the Letal genomic sequence (page 15 at the first full paragraph and page 4 at lines 16-21). The specification also discloses that Letal and functional variants and fragments thereof, can be used, for example to enhance proliferation of immunoeffector cells such as NK and NKT cells and/or CTL activity both *in vitro* and *in vivo*, for example against tumors and infectious agents such as viruses and bacteria, or to expand T cells or other effector cells *in vitro* for use in adoptive immunotherapy for patients with cancer and infectious diseases (paragraph spanning pages 17-18). The specification discloses that sequence identity of Letal with ULBP1, ULBP2 and ULBP3 ranges from 33.3 to 38.5% (page 30 at lines 10-12 and Figure 1B). The specification discloses sequence alignment/identity of SEQ ID NO: 8 with the amino acid sequences of ULBP1, 2 and 3, as well as signal peptide, α1 and α3 domain alignments, but does not disclose what amino acid residues are important for various Letal functional properties.

The claims encompass an isolated nucleic acid molecule that encodes an amino acid sequence that has only one amino acid in common with SEQ ID NO: 8 (a variant) or any fragment of SEQ ID NO: 8 with undisclosed N- and/or -C-terminal amino acid sequences.

Even single amino acid differences can result in drastically altered functions between two proteins. For example, Wang *et al* (JBC 276:49213-49220, 2001) show that a single amino acid determines lysophospholipid specificity of the S1P1 (EDG1) and LPA1 (EDG2) phospholipids growth factor receptors (*e.g.,* abstract). Wang *et al* show that a single amino acid Glu^{121} in S1P1/EDG1, which corresponds to Gln^{125} in LPA1/EDG2, influences the specificity for S1P or LAP (see page 49213 last ¶). Mutating the Arg-Glu-Gly motif to that is conserved among LPA receptors Arg-Gln-Gly, lead to ligand selectivity switch in concert with the mutations.

There is insufficient guidance in the specification as to how to make and/or use instant invention. Undue experimentation would be required of one skilled in the art to practice the instant invention. See In re Wands 8 USPQ2d 1400 (CAFC 1988).

12. For the purpose of prior art rejections, the filing date of the instant claims 9, 10 and 12-18 is deemed to be the filing date of PCT/US03/27488, *i.e.,* 9/4/03, as the provisional parent applications 60/408,397 and 60/478,371 do not support the claimed limitations of the instant application, *i.e.,* a nucleic acid molecule that encodes a polypeptide comprising the sequence of a variant or fragment of SEQ ID NO: 8, including that recited in claim 10.

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

14. Claims 9, 10, 12-14 and 16-18 are rejected under 35 U.S.C. 102(a) as being anticipated by WO 03/029436 A2 (4/10/03).

WO 03/029436 A2 teaches isolated ULBP4 protein, useful fragments thereof, and those having substantial amino acid sequence identity to ULBP4, a nucleic acid molecule encoding ULBP4 and one complementary thereto, a viral vector comprising the said nucleic acid molecule operably linked to a promoter, and a mammalian host cell and method for culturing the host cell to produce the protein (especially abstract, page 3 at paragraphs 2-4 and continuing onto the paragraph on page 4, page 8 at the second paragraph, paragraph spanning pages 8-9, page 23 at paragraphs 2-3, page 24 at paragraphs 1-2, page 25 at paragraphs 2-4, pages 26-28 at the first full paragraph, pages 39-42 at Examples 1-2, claims 12-15, 17, 20-23).

15. Claims 9, 10, 12-14 and16 are rejected under 35 U.S.C. 102(a) as being anticipated by Chalupny *et al* (Biochem. Biophys. Res. Comm. 305: 129-135, 5/23/03, IDS reference).

Chalupny *et al* teach an isolated cDNA encoding ULBP4, a viral vector comprising said cDNA operably linked to a promoter and a host cell comprising said vector (especially materials and methods, Figure 1, page 132 at the second full paragraph at column 2).

16. Claims 9, 10, 12-14 and 16 are rejected under 35 U.S.C. 102(a) as being anticipated by Conejo-Garcia *et al* (Cancer Biol. & Ther. 2(4): e112-e117, July/August, 2003, IDS reference).

Conejo-Garcia *et al* teach isolated cDNA encoding Letal (ULBP4), a retroviral vector comprising the said cDNA operably linked to a promoter, and a host cell comprising said vector (see entire reference, especially Results section at column 2 on page e114 and continuing onto the paragraph at column 1 on page e115).

17. Claims 9, 10, 12-14 and 16-18 are rejected under 35 U.S.C. 102(e) as being anticipated by US 2003/0195337 A1.

WO 03/029436 A2 teaches isolated ULBP4 protein, useful fragments thereof, and those having substantial amino acid sequence identity to ULBP4, a nucleic acid molecule encoding ULBP4 and a complementary nucleic acid thereof, a viral vector comprising the said nucleic acid molecule and a mammalian host cell and method for culturing the host cell to produce the protein, (abstract, [0012]-[0014], [0025], [0046], [0048], [0053], [0063]-[0064], [0072], [0077], [0083], [0085], [0089]-[0090], [0104]-[0108], [0110], [0112]-[0122], Table I on page 16, Examples, claims 12-26).

18. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

19. Claims 9, 10 and 12-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Conejo-Garcia *et al* (Cancer Biol. & Ther. 2(4): e112-e117, July/August, 2003, IDS reference) in view of Katabi *et al* (Human Gene Therapy 10: 155-164, 1999).

During patent examination, the pending claims must be "given the broadest reasonable interpretation consistent with the specification." Applicant always has the opportunity to amend the claims during prosecution and broad interpretation by the Examiner reduces the possibility that the claim, once issued, will be interpreted more broadly than is justified. In re Prater, 162 USPQ 541, 550 - 51 (CCPA 1969).

It is noted by the Examiner that the limitation “tumor specific promoter” is not defined in the instant specification. The specification at [0033] discloses only some examples of tumor specific promoters.

Conejo-Garcia *et al* teach isolated cDNA encoding Letal (ULBP4), a retroviral vector comprising the said cDNA operably linked to a promoter, and a host cell comprising said vector (see entire reference, especially Results section at column 2 on page e114 and continuing onto the paragraph at column 1 on page e115). Conejo-Garcia *et al* further teach that expansion of specific T-cells at tumor sites can be boosted by engineering cells with higher levels of Letal or using soluble forms of the ligand.

Conejo-Garcia *et al* do not teach wherein the promoter is a tumor specific promoter.

Katabi *et al* teach use of tumor-selective, *i.e.,* specific, promoters in targeted gene therapy for cancer (especially abstract and overview summary sections).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used a tumor-specific promoter as taught by Katabi *et al* in the vector construct taught by Conejo-Garcia *et al*.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to expand specific T-cells at tumor sites by engineering cells with higher levels of Letal as taught by Conejo-Garcia *et al*.

20. Claims 9, 10, 12-14 and 16-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Conejo-Garcia *et al* (Cancer Biol. & Ther. 2(4): e112-e117, July/August, 2003, IDS reference) in view of Searle (Curr. Opin. Biotech. 6:548-552, 1995).

Conejo-Garcia *et al* teach isolated cDNA encoding Letal (ULBP4), a retroviral vector comprising the said cDNA operably linked to a promoter, and a host cell comprising said vector (see entire reference, especially Results section at column 2 on page e114 and continuing onto the paragraph at column 1 on page e115). Conejo-Garcia *et al* teach sequence alignment of Letal with ULBP1, 2 and 3, as well as identification of the signal peptide, the α1 and α2 domains ant the transmembrane and cytoplasmic regions (especially Figure 1 and Results). Conejo-Garcia *et al* further teach that expansion of specific T-cells at tumor sites can be boosted by engineering cells with higher levels of Letal or using soluble forms of the ligand. Conejo-Garcia *et al* teach that Letal has a transmembrane and cytoplasmic domain (Figure 1).

Conejo-Garcia *et al* do not teach a method of producing a polypeptide comprising culturing the mammalian host cell of claim 16 under conditions such that said nucleic acid is expressed and said polypeptide is thereby produced.

Searle teaches a method for producing soluble forms of membrane proteins in mammalian cell lines (see entire reference).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have produced soluble forms of the Letal protein taught by Conejo-Garcia *et al* using the expression system taught by Searle.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to produce soluble Letal protein because Conejo-Garcia *et al* teach what nucleic acid sequences encode the extracellular portion *vs* the transmembrane and cytoplasmic portions of Letal, and they further teach boosting expansion of specific T-cells at tumor sites using soluble forms of Letal.

21. Claims 9, 10 and 12-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 03/029436 A2 (4/10/03) in view of Katabi *et al* (Human Gene Therapy 10: 155-164, 1999)

WO 03/029436 A2 teaches isolated ULBP4 protein, useful fragments thereof, and those having substantial amino acid sequence identity to ULBP4, a nucleic acid molecule encoding ULBP4 and a complementary nucleic acid thereto, a viral vector comprising the said nucleic acid molecule operably linked to a promoter, and a mammalian host cell and method for culturing the host cell to produce the protein (especially Abstract, page 3 at paragraphs 2-4 and continuing onto the paragraph on page 4, page 8 at the second paragraph, paragraph spanning pages 8-9, page 23 at paragraphs 2-3, page 24 at paragraphs 1-2, page 25 at paragraphs 2-4, pages 26-28 at the first full paragraph, pages 39-42 at Examples 1-2, claims 12-15, 17, 20-23). WO 03/029436 A2 teaches that it is desirable to increase the number of ULBP4 proteins localized near or on the surface of a cancer cell, which may or may not express a ULBP4 protein (page 34 at the first full paragraph).

WO 03/029436 A2 does not teach wherein the promoter is a tumor specific promoter.

Katabi *et al* teach use of tumor-selective, *i.e.,* specific, promoters in targeted gene therapy for cancer (especially abstract and overview summary sections).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used a tumor-specific promoter as taught by Katabi *et al* in the vector construct taught by WO 03/029436 A2.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to increase the number of ULBP4 protein at the cell surface, especially as per the teaching of WO 03/029436 A2 of the desirability of doing so.

22. Claims 9, 10 and 12-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chalupny *et al* (Biocehm. Biophys. Res. Comm. 305: 129-135, 5/23/03, IDS reference) in view of Katabi *et al* (Human Gene Therapy 10: 155-164, 1999) and Conejo-Garcia *et al* (Cancer Biol. & Ther. 2(4): e112-e117, July/August, 2003, IDS reference) and Searle (Curr. Opin. Biotech. 6:548-552, 1995).

Chalupny *et al* teach an isolated cDNA encoding ULBP4 (*i.e.,* Letal), a viral vector comprising said cDNA operably linked to a promoter and a host cell comprising said vector (especially materials and methods, Figure 1, page 132 at the second full paragraph at column 2).

Chalupny *et al* do not teach wherein the promoter is a tumor specific promoter.

Katabi *et al* teach use of tumor-selective, *i.e.,* specific, promoters in targeted gene therapy for cancer (especially abstract and overview summary sections).

Conejo-Garcia *et al* teach isolated cDNA encoding Letal (ULBP4), a retroviral vector comprising the said cDNA operably linked to a promoter, and a host cell comprising said vector (see entire reference, especially Results section at column 2 on page e114 and continuing onto the paragraph at column 1 on page e115). Conejo-Garcia *et al* further teach that expansion of specific T-cells at tumor sites can be boosted by engineering cells with higher levels of Letal or using soluble forms of the ligand.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have used a tumor-specific promoter/vector construct as taught by Katabi *et al* in place of the one taught by Chalupny *et al*.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order target ULBP4 to a tumor cell to boost levels of Letal as taught by Conejo-Garcia *et al*.

Searle teaches a method for producing soluble forms of membrane proteins in mammalian cell lines (see entire reference).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have produced soluble forms of the Letal protein taught by Chalupny *et al* using the expression system taught by Searle.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to produce soluble Letal protein because Conejo-Garcia *et al* teach what nucleic acid sequences encode the extracellular portion *vs* the transmembrane and cytoplasmic portions of Letal, and they further teach boosting expansion of specific T-cells at tumor sites using soluble forms of Letal.

23. Claims 9, 10 and 12-18 are objected to because of the following informality: the claims (9, 10, 12, 14 and 18) recite "isolated nucleic acid" rather than "nucleic acid molecule." Appropriate correction is required.

24. No claim is allowed.

25. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Eileen B. O'Hara, can be reached on 571-272-0878. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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